

Radio-Chemotherapy as a Preoperative Treatment for Advanced Rectal Cancer. Evaluation of Down-Staging and Morbidity

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Key Words

Rectal cancer · Ionizing irradiation · Chemotherapy · Down-staging · Acute side effects

Summary

Background: The standard therapy for patients with clinically resectable rectal cancer is generally considered to be surgery. If the patient is diagnosed with advanced disease, postoperative radio-chemotherapy (RCT) is usually recommended. In our study we aimed to investigate and analyze the effectiveness and toxicity of preoperative pelvic radiotherapy in combination with 5-fluorouracil (5-FU) in locally advanced rectal cancer. **Patients and Methods:** From June 1999 to September 2001 we evaluated 50 consecutive patients [37 male and 13 female; average age 65.1 (range 46–79.5) years] with locally advanced rectal carcinoma. 32 patients were staged as uT3, 14 as uT4, and 4 as uT2. Regarding N-staging, 22 patients were diagnosed as uN0. 2 patients had distant metastases, with liver metastases in both instances. Conformal irradiation was performed with a box technique (4-field technique) with a dose of 45 Gy (5×1.8 Gy per week for a total of 25 sessions). From days 1–5 and 29–33, all patients received 5-FU (500 mg/m² per day, as a continuous i.v. injection). **Results:** Remission was observed in 28 patients (56%), with down-staging of at least one T-stage. A better success rate was achieved for patients with deep-seated tumors (64% of the patients in this group). Complete remission was observed in 4 patients (8.0%) and progression in 3 (6.0%). 15 patients had no detectable change in tumor staging (30.0%). A surgical R0 resection could be achieved in 43 patients, an R1 resection (minimal margin) in 7. Side effects and toxicity (common toxicity criteria) of RCT included grade I-II dysuria in 5 patients (10%), grade I-II diarrhea in 20 patients (40%), and severe diarrhea in 2 patients (4.0%). Grade I-II skin reaction was noticed in 22 patients (44.0%), severe skin reaction only in 1 patient. Regarding acute postoperative morbidity, abscess and fistula formation was noted in 8 patients (16.0%), with anastomosis leakage in 7 (14%). **Conclusion:** Preoperative radiotherapy appears to be a feasible therapeutic approach with moderate toxicity and the potential to induce down-staging. The data presented in this study confirm the preliminary reports on this neoadjuvant treatment.

Schlüsselwörter

Rektumkarzinom · Ionsierende Bestrahlung · Chemotherapie · Down-Staging · Akute Nebenwirkungen

Zusammenfassung

Hintergrund: Bei Patienten mit operablem Rektumkarzinom gilt als Standardbehandlung nach wie vor die chirurgische Resektion. Für Patienten in fortgeschrittenem Krankheitsstadium wird eine postoperative Radio-Chemotherapie (RCT) empfohlen. Ziel der vorliegenden Arbeit ist es, die Effektivität und Toxizität bei präoperativer Bestrahlung in Kombination mit 5-Fluorouracil (5-FU) bei lokal fortgeschrittenem Rektumkarzinom zu untersuchen. **Patienten und Methoden:** Im Zeitraum von Juni 1999 bis September 2001 wurden 50 Patienten (13 weiblich, 37 männlich) mit lokal fortgeschrittenem Rektumkarzinom untersucht. Der Altersdurchschnitt betrug 65,1 (Bereich 46–79,5) Jahre, 32 Patienten hatten einen uT3-Tumor, 14 Patienten einen uT4- und die restlichen 4 Patienten einem uT2-Tumor. In Bezug auf den Lymphknotenstatus lag bei 22 Patienten ein N0-Stadium vor. 2 Patienten hatten Lebermetastasen. Die Strahlentherapie wurde konform über eine 4-Felder-Box-Technik bis zu einer Gesamtdosis von 45,0 Gy (25 Fraktionen mit $5 \times 1,8$ Gy pro Woche) appliziert. An den Tagen 1–5 und 29–33 erhielten die Patienten 5-FU-Chemotherapie (500 mg/m² pro Tag als Dauerinfusion). **Ergebnisse:** Bei 56% der Patienten (n = 28) wurde eine pathologische Remission um mindestens ein T-Stadium erreicht, mit bessem Erfolg bei tief sitzenden Tumoren (64,0% der Patienten in dieser Gruppe). Eine komplette Remission trat bei 4 Patienten (8,0%) und ein Progress bei 3 Patienten (6,0%) auf. Im Rahmen der Operation wurde bei 43 Patienten eine R0-Resektion erreicht, bei 7 Patienten eine R1-Resektion (mikroskopischer Tumorrest). Die Toxizität (common toxicity criteria) im Rahmen der RCT bestand aus Dysurie Grad I-II bei 5 Patienten (10,0%), Diarrhoe Grad I-II bei 20 Patienten (40,0%) und schwerer Diarrhoe nur bei 2 Patienten (4,0%). Hautreaktionen Grad I-II traten bei 22 Patienten (44,0%) auf, schwerere Hautreaktionen nur bei einem Patienten. Die akute postoperative Morbidität bestand aus Abszess- oder Fistelbildung bei 8 Patienten (16,0%), Anastomoseninsuffizienz bei 7 Patienten (14,0%). **Schlussfolgerung:** Als Ergebnis kann festgehalten werden, dass die präoperative RCT mit moderater Toxizität durchführbar ist und eine Tumorverkleinerung bewirken kann. Die Ergebnisse dieser Arbeit bestätigen die vorläufigen Daten anderer Arbeiten über das neoadjuvante Behandlungskonzept.

Introduction

Colorectal cancer is one of the leading cancer-related causes of death. In Germany, the incidence of colorectal carcinoma amounts to 55,000–60,000 cases per year, one third of which are rectal cancers. The mainstay of therapy has over the past 100 years been surgical resection. However, for the majority of rectal cancers treated conventionally by resection alone, locoregional recurrences are the major mode of failure [1]. Over the past decades, significant progress has been made in developing effective adjuvant regimens. During the last decade, substantial advances have been made with respect to treatment modalities and surgical management with a shift from radical operations to innovative sphincter-preserving techniques.

Postoperative combined-modality therapy has significantly contributed to improving local control and survival of patients. The local recurrence rate has been reduced dramatically with the use of radiotherapy, especially when combined with chemotherapy. Preoperative therapy (combined radio- and chemotherapy) has the potential advantages of producing less acute toxicity and increasing the possibility of sphincter preservation. Preoperative radiotherapy is becoming the standard of care for resectable, locally advanced adenocarcinoma of the rectum, being no longer limited to selected specialized cancer centers [2]. New and improved radiation techniques with conformal radiation and modern chemotherapeutic regimens may have the potential to further increase the therapeutic benefit.

Various reports on adjuvant treatment of advanced locoregional rectal carcinoma have been published, evaluating various radiation doses and chemotherapy regimens [3–11]. The irradiation regimen varies from 25 Gy fractionated in 5 sessions (hypofractionated radiotherapy) [10, 11] to conventional treatment between 36 and 50.4 Gy [3–9]. Some reports also combined preoperative with postoperative irradiation [7], others evaluated a combination treatment with hyperthermia [9]. All protocols included chemotherapeutic regimens, especially 5-fluorouracil (5-FU) and leucovorin. They differ, however, regarding the application modes and chemotherapy doses.

The pretreatment diagnosis is generally based on computed tomography (CT) [12], magnetic resonance imaging (MRI) [13, 14] or ultrasound (US) [15]. The effectiveness of MRI in comparison to CT has previously been demonstrated [14].

The objective of our current study is to evaluate down-staging and morbidity in the preoperative treatment of locoregionally advanced, rectal cancer with combined radio- and chemotherapy. In this nonrandomized retrospective study the morbidity and feasibility of this application method was analyzed. The study analysis was based on the ARO/AIO/CAO trial [6].

Table 1. Patient characteristics

Age, years	
Median	64.1
Range	46–79.5
Gender, f/m	13/37
Stage	
Dukes B	26
Dukes C	24
Grading	
G1	2
G2	42
G3	6
Tumor distance from anal verge	
≤5 cm	25
>5 cm	25

Material and Methods

From June 1999 to September 2001 we evaluated 50 consecutive patients (37 male, 13 female) with an average age of 65.1 (range 46–79.5) years. All patients had been diagnosed with locally advanced rectal cancer. 32 patients suffered from a uT3 tumor, 14 patients had a uT4 and 4 patients a uT2 stage. Regarding N-staging, 24 patients were diagnosed as uN0 (table 1). Histological grading was rated G2 in 42 patients, G3 in 6 patients, and high-grade dysplasia in 2 patients. Staging was based on computed tomography (CT), magnetic resonance imaging (MRI) and endosonography [12–15]. Biopsies were taken during coloscopic control.

In 25 patients (50.0%) the tumor was localized up to 5 cm from the anal verge (deep-seated tumor); in the remainder it was located more than 5 cm from the anal verge (high-seated tumor).

The patients were selected for preoperative irradiation based on staging results. The inclusion criteria were locally advanced rectal cancer with tumors that either penetrated the muscular layer of the bowel wall or the entire bowel wall (modified Dukes stages B) or spread to the lymph nodes in the same region (Dukes stages C).

Irradiation was applied using conformal irradiation with a box technique (4-field technique) up to a dose of 45 Gy (5 × 1.8 Gy per week for a total number of 25 sessions). From days 1–5 and days 29–33, the patients received 5-FU (500 mg/m² per day, 24-hour continuous infusion as is customary in our institution). 5-FU is a known radiosensitizer for rectal cancers. However, the dose to be applied varies among the different studies [3–6]. Based on published data [16], all patients underwent surgical intervention 6–8 weeks after radiochemotherapeutic treatment (RCT). 11 patients had an abdominoperineal rectal extirpation. The remaining 39 patients underwent deep anterior rectal resection with total mesorectal excision.

An updated clinical re-staging with CT or MRI was performed in 37 patients shortly after termination of therapy. The remaining 13 patients were operated in other hospitals and were not re-evaluated with CT and/or MRI. The following parameters were evaluated: (1) clinical remission after treatment, based upon CT and/or MRI results [12–15]; (2) pathological remission after treatment based upon histological results after surgery; (3) complication rate caused by RCT; (4) postoperative morbidity. No evaluation of survival rate was done due to the short follow-up time. Morbidity and side effects were evaluated according to common toxicity criteria (CTC [17, 18]).

Results

The clinical evaluation after RCT including CT and/or MRI findings demonstrated the following: In 15 patients no change

Table 2. Clinical evaluation after RCT (based on CT or MR imaging). Subdivision between patients with tumor distance from anal verge ≤ 5 cm and those with tumor distance from anal verge > 5 cm.

	No change		Partial remission		Complete remission		Progression	
	n	%	n	%	n	%	n	%
Tumor distance from anal verge								
≤ 5 cm	6	30.0	10	50.0	2	10.0	2	10.0
> 5 cm	9	52.9	7	41.2	1	5.9		
<i>Overall</i>	15	40.5	17	45.9	3	8.1	2	5.4

Table 3a. Pathological evaluation after RCT and tumor resection in comparison with the clinical pretreatment status

	No change		Partial remission		Complete remission		Progression	
	n	%	n	%	n	%	n	%
Deep-seated tumor	7	28.0	12	48.0	3	12.0	3	12.0
High-seated tumor	8	32.0	16	64.0	1	4.0		
<i>Overall</i>	15	30.0	28	56.0	4	8.0	3	6.0

Table 3b. Patients with pathologically confirmed partial remission, classified in tumor remission, lymph node remission, and remission in both

Partial remission in	n	%
Tumor	16	32.0
Lymph nodes	6	12.0
Tumor and lymph nodes	6	12.0
<i>Overall</i>	28	50.0

was observed (40.5%); this held particularly true for patients with deep-seated tumors (table 1). Partial clinical remission (at least one T-stage) was noticed in 45.9% of patients, with better results for high-seated tumors (50% of patients, table 2). Complete clinical remission was observed in only 3 patients (8.1%). Clinical progression was encountered in 2 patients with high-seated tumors (5.4%).

Pathological remission as compared to preoperative clinical staging was noticed in 28 patients (56.0%), with improvement of at least one T-stage (64.0% of the patients in this group) (table 3). A higher success rate was noticed in deep-seated tumors. Complete remission was observed in 4 patients (8.0%), while progress was demonstrated in 3 patients (6.0%); in 15 patients (30.0%) no change in tumor staging was observed. Surgical intervention achieved an R0 resection in 42 patients and an R1 resection in 8 patients (minimal margin).

The toxicity of RCT was also evaluated according to CTC [17, 18] (table 4). Grade I-II dysuria was seen in 5 patients (10.0%) and grade I-II diarrhea in 20 patients (40.0%). Severe diarrhea was observed in only 2 patients (4.0%), while a grade I-II skin reaction was noticed in 22 patients (44.0%). A severe skin reaction was found in only 1 patient.

The assessment of acute postoperative morbidity showed (table 5) abscess and fistula formation in 8 patients (16.0%); in

7 of these patients a leakage of the anastomosis site was noted (14.0%). Other side effects were delayed wound healing (6.0%), bleeding (3 patients), and cardiac complications (2 patients). Avulsion of the anal ampulla was seen in 1 patient, probably because of concrescence. Organ insufficiency was observed in 1 patient shortly after the surgical intervention.

Discussion

Although preoperative chemo-irradiation for locally advanced and high-risk rectal cancer improves the local recurrence rate [19–20], its adverse effects are not well defined. Differing reports on treatment regimens are the main problem [3–11]. Previous reports have demonstrated that neoadjuvant therapy is a well-tolerated treatment for adenocarcinoma of the rectum and that it may produce substantial down-staging and a highly curative resection rate. Nevertheless, the optimal timing of surgery after preoperative RCT in rectal cancer is unknown [16]. The study published by François et al. [16] proposed an interval between 6 and 8 weeks as opposed to a shorter interval of 2 weeks.

Chemo-irradiation has the potential to achieve a high response rate, even though the toxicity of this treatment can

Table 4. Acute radiation-induced toxicities (following CTC scoring criteria)

Organ tissue	Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%
Skin	12	24	10	20	1	2	—	—
Genitourinary	4	8	1	2	—	—	—	—
Lower gastrointestinal, including pelvis	12	24	8	16	2	4	—	—

Table 5. Peri- and postoperative complications

Complication	n	%
Anastomosis leak	7	14.0
Abscess / fistula	8	16.0
Delay in wound healing	3	6.0
Bleeding	3	6.0
Cardiac complications	2	4.0

sometimes be high. Some multicenter trials [5–7, 19–23] have aimed to evaluate the feasibility, morbidity and survival rate after preoperative RCT. A comparison of these trials is not easily done, since various treatment modalities, such as differing radiation doses (e.g. 5 × 5 Gy in the Dutch and Swedish trial, or 45–50.4 Gy in the CAO/ARO/AIO-94 trial) [6, 21, 22] and different administration routes of chemotherapy, were applied. Most of the studies published so far used 5-FU and leucovorin as both radiosensitizers and chemotherapy; however, the dosage applied and the administration routes differed. All trials were able to demonstrate the safety and feasibility of neoadjuvant RCT. Bosset et al. [23] could demonstrate a 5-year disease-free survival in 92% of patients with T3M0 rectal cancer, when preoperative RCT was performed. The advantages of RCT as opposed to radiotherapy alone are already well known and accepted [3–11]. The most frequently used radiosensitizer is 5-FU. However, the dosage to be administered and the duration of the application are still subject to dispute. The applied doses vary between 225 and 1,000 mg/m² [6, 23, 24]. Attempts to find other radiosensitizers [25] demonstrated Tagefur to have advantages over 5-FU in the treatment of rectal cancer. A recent report [26] suggested that the combination of oxaliplatin and irinotecan may have the potential to further increase the therapeutic benefit of rectal cancer. The basic issue of timing (pre- or postoperative) within a multimodal regimen is currently under investigation. However, several reports were not able to demonstrate significant down-staging after preoperative treatment [11]; it needs to be taken into consideration, though, that the treatment regimens reported in these studies included irradiation regimens of 5 × 5 Gy and surgical intervention within 10 days after RCT. In

comparison, other reported treatment regimens applied 40–50.4 Gy and performed surgery 4–6 weeks after preoperative treatment [3–10]. With modern radiation techniques, preoperative radiotherapy can be delivered without any substantial increase in postoperative mortality or morbidity and with a low rate of late toxicity, provided that the radiation technique is optimal.

Our results correlated well with the above-mentioned literature in that they achieved clinical and pathological down-staging in 45.9 and 56.0% of cases, respectively. The complete remission rate was low (8.1% clinical and 8.0% pathological) as is to be expected for locally advanced tumor. The correlation between clinical and pathological staging is also confirmed and corresponds to the already known literature [12–15].

The most common form of acute toxicity encountered during adjuvant pelvic irradiation is diarrhea (approximately 24% of the patients). Skin reaction (perineal dermatitis) is also known (approximately 30–40%) [27]. The postoperative morbidity, such as anastomotic leak (14.0%) and abscess formation (16.0%), was higher as compared to reports on postoperative irradiation regimens [6]. Bleeding and delay of wound healing were the same in our preoperative group in comparison to postoperative irradiation reports [6].

Our nonrandomized retrospective study analyzed the morbidity and feasibility of this application method. A long-term survival rate evaluation was not possible as yet, since follow-up times were still short, with a mean of 7.6 (range 3–26) months. In conclusion, preoperative radiotherapy is a feasible method with moderate toxicity and a potential to induce down-staging. Our data confirm the preliminary reports about this neoadjuvant treatment.

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